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Effect of endurance exercise training on heart rate onset and heart rate recovery responses to submaximal exercise in animals susceptible to ventricular fibrillation

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Billman GE, Kukielka M. Effect of endurance exercise training on heart rate onset and heart rate recovery responses to submaximal exercise in animals susceptible to ventricular fibrillation. J Appl Physiol 102: 231–240, 2007. First published September 28, 2006; doi:10.1152/japplphysiol.00793.2006.—Both a large heart rate (HR) increase at exercise onset and a slow heart rate (HR) recovery following the termination of exercise have been linked to an increased risk for ventricular fibrillation (VF) in patients with coronary artery disease. Endurance exercise training can alter cardiac autonomic regulation. Therefore, it is possible that this intervention could restore a more normal HR regulation in high-risk individuals. To test this hypothesis, HR and HR variability (HRV, 0.24–to 1.04-Hz frequency component; an index of cardiac vagal activity) responses to submaximal exercise were measured 30, 60, and 120 s after exercise onset and 30, 60, and 120 s following the termination of exercise in dogs with healed myocardial infarctions known to be susceptible (n = 19) to VF (induced by a 2-min coronary occlusion during the last minute of a submaximal exercise test). These studies were then repeated after either a 10-wk exercise program (treadmill running, n = 10) or an equivalent sedentary period (n = 9). After 10 wk, the response to exercise was not altered in the sedentary animals. In contrast, endurance exercise increased indexes of cardiac vagal activity such that HR at exercise onset was reduced (30 s after exercise onset: HR pretraining 179 ± 8.4 vs. posttraining 151.4 ± 6.6 beats/min; HRV pretraining 4.0 ± 0.4 vs. posttraining 5.8 ± 0.4 ln ms²), whereas HR recovery 30 s after the termination of exercise increased (HR pretraining 186 ± 7.8 vs. posttraining 159.4 ± 7.7 beats/min; HRV pretraining 2.4 ± 0.3 vs. posttraining 4.0 ± 0.6 ln ms²). Thus, endurance exercise training restored a more normal HR regulation in dogs susceptible to VF.

Parasympathetic nervous system; myocardial ischemia; myocardial infarction

Both a large heart rate increase at exercise onset and a slow heart rate recovery (i.e., the time required for heart rate to return to preexercise values) following the termination of exercise have been linked to an increased susceptibility to ventricular fibrillation in patients with ischemic heart disease. For example, an elevated heart rate increase at the onset of exercise has been linked to an increased risk for adverse cardiovascular events, including death (16). Patients with documented coronary artery disease that exhibited the largest increase in heart rate at exercise onset also had a greater risk for cardiac events (cardiac deaths and nonfatal myocardial infarctions) than did those subjects with a more modest heart rate increase (16). In a similar manner, heart rate recovery after exercise has been shown to be an independent predictor of mortality across substantial and diverse population groups (12, 23, 29–32). Cole et al. (12) demonstrated in a multicenter study of 5,234 individuals that abnormal heart rate recovery after submaximal exercise predicted death, even after adjustment for various confounding factors; Nishime et al. (32) published similar results from a total of 9,454 patients.

Our laboratory recently demonstrated that dogs confirmed to be susceptible to ventricular fibrillation (induced by a 2-min coronary artery occlusion during the last minute of an 18-min submaximal exercise test) also exhibited both an elevated heart rate response to the onset of exercise (4) and a slower heart rate recovery following the cessation of exercise (42) than did those animals that were resistant to malignant arrhythmias. Heart rate variability (an index of cardiac vagal activity) was depressed to a greater extent in the susceptible compared with the resistant dogs, and furthermore, both the heart rate recovery and heart rate variability differences were eliminated by prior treatment with the cholinergic antagonist atropine (42). As such, the attenuated heart rate recovery seen in the animals subsequently shown to be susceptible to ventricular fibrillation almost certainly resulted from reduced parasympathetic recovery after exercise. In a similar fashion, exercise onset provoked larger increases in heart rate in dogs susceptible to ventricular fibrillation than in animals resistant to these malignant arrhythmias, and furthermore, these differences were completely eliminated by the prior treatment with propranolol (4). These studies suggest that animals susceptible to ventricular fibrillation exhibit differing autonomic responses to exercise onset and the termination of exercise. The animals susceptible to ventricular fibrillation displayed an enhanced sympathetic activation at the onset of exercise but an impaired cardiac parasympathetic reactivation following exercise.

It is well established that regular exercise can improve cardiac autonomic balance (increasing parasympathetic while decreasing sympathetic regulation of the heart) (2, 11, 17, 27, 41, 43, 45). In both humans and animals, heart rate at submaximal workloads is lower in trained individuals compared with sedentary controls (2, 8, 11, 41), whereas the presence of a resting bradycardia is frequently used to confirm that training has been effective (17, 27, 43, 45). Exercise training programs can also increase heart rate variability in patients (25, 26, 28, 34, 36) and animals (8) recovering from myocardial infarction, and it may reduce the incidence of sudden death and arrhythmias in both human and animal models (8–10, 25, 33, 34, 39). We recently demonstrated that endurance exercise training...
improved cardiac autonomic regulation in dogs confirmed to be susceptible to ventricular fibrillation by both enhancing cardiac parasympathetic regulation (8) and decreasing β2-adrenoceptor sensitivity (10). Furthermore, exercise training completely suppressed ventricular fibrillation induced by myocardial ischemia (8–10). However, the effects of endurance exercise training on the heart rate response to exercise onset or the heart rate recovery following the termination of exercise were not investigated in these studies.

It was therefore the purpose of this study to evaluate the effects of endurance exercise training on the heart rate and the heart rate variability responses to the onset and the termination of exercise in dogs confirmed to be susceptible to ventricular fibrillation. In particular, the hypothesis that endurance exercise training would both decrease the heart rate response to the onset of submaximal exercise and accelerate the heart rate recovery (i.e., a faster return toward preexercise values) following exercise in these dogs, thereby restoring a more normal (i.e., similar to healthy/electrical stable hearts) cardiac autonomic regulation in the animals susceptible to ventricular fibrillation, was tested. Time series analysis of heart rate variability was used as an index of cardiac parasympathetic regulation in dogs with healed myocardial infarction that were subsequently found to be susceptible to ventricular fibrillation induced by acute myocardial ischemia.

METHODS

The principles governing the care and use of animals as expressed by the Declaration of Helsinki, and as adopted by the American Physiological Society, were followed at all times during this study. In addition, the Ohio State University Institutional Animal Care and Use Committee approved all the procedures used in this study.

Ventricular fibrillation was induced by a 2-min coronary occlusion during the last minute of an 18-min submaximal exercise test in 26 dogs with healed myocardial infarctions (see below). Three animals were not successfully defibrillated. In addition, four dogs (all in the sedentary group) died during the 10-wk sedentary period (see below). Thus archived data from 19 female heartworm-free purpose-bred mongrel dogs (weight 19.1 ± 0.5 kg, age 2–3 yr) that had been shown previously (3, 8, 10) or an equivalent sedentary period (susceptible, n = 10) or an equivalent sedentary period (susceptible, n = 9). The dogs in the exercise training group ran on a motor-driven treadmill for 10 wk, 5 days/wk, at 20–70% of maximum heart rate. The exercise training protocol has been previously described (8, 10). Briefly, exercise intensity and duration progressively increased as follows: 1st wk, 20 min at 4.8 kph/0% grade; 2nd wk, 40 min at 5.6 kph/10% grade; 3rd wk, 40 min at 6.4 kph/10% grade; 4th wk, 60 min at 6.4 kph/10% grade; 5th wk, 60 min at 6.4 kph/12% grade; 6th wk, 75 min at 6.4 kph/12% grade; 7th wk, 90 min at 6.4 kph/12% grade; 8th to 10th wk, 90 min at 6.4 kph/14% grade. Each exercise session included 5-min warm-up and 5-min cooldown periods (running at a low intensity, 0% grade and speed, 4.8 kph). The dogs in the sedentary group were placed in transport cage for equivalent time periods but without exercise. The effectiveness of the exercise training program was evaluated by measuring left ventricular wall thickness (before and after training using echocardiography), skeletal muscle citrate synthase activity (from samples obtained when the animals were euthanized, and the heart rate response to submaximal (comparison before and after the 10-wk exercise or 10-wk sedentary period) as previously described (8, 10).

Heart rate variability protocols. The studies began 3–4 wk after the production of the myocardial infarction. First, over the period of 3–5 days, the dogs learned to run on a motor-driven treadmill. The cardiac response to submaximal exercise was then evaluated as follows: exercise lasted a total of 18 min with workload increasing every 3 min. The protocol began with a 3-min warm-up period, during which the dogs ran at 4.8 kilometers per hour (kph) at 0% grade. The speed was then increased to 6.4 kph, and the grade increased every 3 min (0, 4, 8, 12, and 16%). The submaximal exercise test was repeated three times (1 time per day). Heart rate and heart rate variability (an index of cardiac vagal activity) were monitored continuously throughout the exercise studies. These studies were repeated after the completion of the 10-wk exercise training or the 10-wk sedentary time period.

The effects of atropine on the heart rate response to the termination of exercise was also evaluated in sedentary (n = 6) and exercise-trained (n = 7) animals both before and at the end of the 10-wk exercise training or sedentary period (see below). A catheter was placed in a cephalic vein so that atropine sulfate (50 μg/kg, Schauberg Pharmaceutical Partners, Schauberg, IL) could be administered while the dogs were running. The treadmill was stopped ∼2–3 min after the atropine had been given (i.e., after a new steady state had been achieved).

Exercise plus ischemia test: classification of the dogs. The susceptibility to ventricular fibrillation was tested as previously described (3–5, 7–10, 41). Briefly, the animals ran on a motor-driven treadmill while workload progressively increased until a heart rate of 70% of maximum (∼210 beats/min) had been achieved. During the last minute of exercise, the left circumflex coronary artery was occluded, the treadmill was stopped, and the occlusion was maintained for an additional minute (total occlusion time = 2 min). Left circumflex coronary blood flow was recorded to confirm that the coronary occlusion was effective (i.e., flow velocity went to zero). The exercise plus ischemia test reliably induced ventricular flutter that rapidly deteriorated into ventricular fibrillation. Therefore, large defibrillation electrodes (Stat-padz, Zoll Medical, Burlington, MA) were placed across the animal’s chest so that electrical defibrillation (Zoll M series defibrillator, Zoll Medical) could be achieved with a minimal delay but only after the animal was unconscious (10–20 s after the onset of ventricular fibrillation). The occlusion was immediately released if ventricular fibrillation occurred. As was previously stated, all 19 dogs used in the present study developed ventricular fibrillation during this exercise plus ischemia test. This test was repeated twice (at least 7 days apart) before assigning the animals to either the exercise training or sedentary groups.

Exercise training protocol. The susceptible (n = 19) dogs were randomly assigned to either a 10-wk exercise training period (susceptible, n = 10) or an equivalent sedentary period (susceptible, n = 9).

The dogs in the exercise training group ran on a motor-driven treadmill for 10 wk, 5 days/wk, at 20–70% of maximum heart rate. The exercise training protocol has been previously described (8, 10). Briefly, exercise intensity and duration progressively increased as follows: 1st wk, 20 min at 4.8 kph/0% grade; 2nd wk, 40 min at 5.6 kph/10% grade; 3rd wk, 40 min at 6.4 kph/10% grade; 4th wk, 60 min at 6.4 kph/10% grade; 5th wk, 60 min at 6.4 kph/12% grade; 6th wk, 75 min at 6.4 kph/12% grade; 7th wk, 90 min at 6.4 kph/12% grade; 8th to 10th wk, 90 min at 6.4 kph/14% grade. Each exercise session included 5-min warm-up and 5-min cooldown periods (running at a low intensity, 0% grade and speed, 4.8 kph). The dogs in the sedentary group were placed in transport cage for equivalent time periods but without exercise. The effectiveness of the exercise training program was evaluated by measuring left ventricular wall thickness (before and after training using echocardiography), skeletal muscle citrate synthase activity (from samples obtained when the animals were euthanized, and the heart rate response to submaximal (comparison before and after the 10-wk exercise or 10-wk sedentary period) as previously described (8, 10).

Data analysis. All data are reported as means ± SE. The data were digitized (1 kHz) and recorded using a Biopac MP-100 data acquisition system (Biopac Systems, Goleta, CA). Heart rate variability was obtained using a Delta-Biotmetrics vagal tone monitor triggering off the ECG R-R interval (Urbana-Champaign, IL). This device employs the time-series signal processing techniques as developed by Porges to estimate the amplitude of respiratory sinus arrhythmia (38). Details of this analysis have been described previously (6). Briefly, the ECG signal was digitized at 1 kHz, and sequential R-R intervals were timed to the nearest millisecond. The nonperiodic baseline fluctuations were
removed using a moving third-order 21-point polynomial function. This procedure prevented leakage of trends and harmonics of nonsinusoidal periodic activity (i.e., transient changes) into the respiratory frequency component. Once the “filtering” procedures had been performed, the output of the moving polynomial was processed with a digital band-pass filter to extract the variance in the 0.24- to 1.04-Hz frequency band. The variance measure was then transformed to its natural logarithm to “normalize” the distribution of the variance estimates to limit the impact of large differences (i.e., outlying values).

Heart rate and heart rate variability (an index of cardiac vagal activity) data were averaged over 30-s intervals, beginning 3 min before the exercise onset and ending 3 min after the termination of the 18-min exercise session. The following time points were evaluated in the present study: for exercise onset, the last 30 s before the onset of exercise, from 0 to 30 s after exercise onset, from 30 to 60 s after exercise onset, and from 90 to 120 s after exercise onset; for heart rate recovery, the last 30 s of exercise, from 0 to 30 s after exercise termination, from 30 to 60 s after exercise termination, and from 90 to 120 s after the termination of exercise. These average values are reported as times 0, 30, 60, and 120 s, respectively. The following three indexes of heart rate variability were determined: vagal activity index, the high-frequency (0.24–1.04 Hz) component of the R-R interval variability; SD of R-R interval; and R-R interval range. The data were compared using ANOVA for repeated measures (NCSS statistical software, Kaysville, UT). For example, the effect of exercise training (or the 10-wk sedentary time period) on the heart rate variability (heart rate; vagal tone index, i.e., 0.24- to 1.04-Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range) response to exercise onset (or exercise termination) were analyzed using a two-way ANOVA (pretraining-posttraining (2 levels) × time (4 levels)) with repeated measures on both factors (pre-post and time). Because repeated-measures ANOVA depends on the homogeneity of covariance, this sphericity assumption (i.e., the assumption that the variance of the difference scores in a within-subject design are equal across the groups) was tested using Mauchley’s test (21). If the sphericity assumption was violated, then the F-ratio was corrected using Huynh-Feldt correction (21). If the F-ratio was found to exceed a critical value (P < 0.05), then the difference between the means was determined using Scheffe’s test. The citrate synthase activity data were compared using Student’s t-test.

RESULTS

Exercise onset responses: training effects. The heart rate and the heart rate variability responses to exercise onset before and after exercise training are shown in Fig. 1, while the same data before and at the end of the 10-wk sedentary period are shown in Fig. 2. These data were obtained during the first stage of the exercise stress test (i.e., with the animals running at 4.8 kph/0% grade). Exercise onset elicited a significant increase in heart rate (time effect, F_3,27 = 73.81, P < 0.0001) with larger increases (pretraining-posttraining effect, F_1,9 = 8.96, P < 0.02) noted in the susceptible dogs before training compared with the same animals after the completion of the exercise
training (Fig. 1). For example, the heart rate increase elicited by exercise onset was significantly smaller (pretraining-posttraining \( F_{3,27} = 3.44, P < 0.03 \)) following exercise training (e.g., change 30 s after exercise onset pretraining vs. posttraining heart rate) than was noted in the same animals before the training had begun.

The heart rate increase was accompanied by corresponding reductions in all three indexes of heart rate variability as displayed in Fig. 1. For example, exercise onset provoked large reductions (time effect, \( F_{3,27} = 28.94, P < 0.0001 \)) in the high-frequency component of the R-R interval variability (a marker of cardiac vagal regulation, 0.24–1.04 Hz) with smaller (pretraining-posttraining effect \( F_{1,9} = 12.13, P < 0.007 \)) reductions noted after exercise training. Despite a higher pre-exercise onset value for this index of cardiac vagal activity, exercise elicited similar [pretraining-posttraining \( F_{3,27} = 0.99, P = 0.41 \), not significant (NS)] changes in this variable in the trained dogs before and at the end of the exercise training program (cardiac vagal activity index decrease 60 s after exercise onset: pretraining vs. posttraining -2.3 ± 0.5 ln ms\(^2\)). Similar results were obtained for R-R interval range and standard deviation of R-R interval (see Fig. 1).

In contrast, although exercise onset provoked significant increases in heart rate (\( F_{3,24} = 45.07, P < 0.0001 \)) and reductions in heart rate variability (e.g., vagal activity index, \( F_{3,24} = 20.78, P < 0.0001 \)), these changes were not altered during the 10-wk sedentary period (pretraining-posttraining effect: heart rate, \( F_{1,8} = 1.08, P = 0.33 \), NS; cardiac vagal activity index, \( F_{1,8} = 4.05, P = 0.08 \), NS).

When considered together, these data suggest that exercise training enhanced cardiac vagal activity and attenuated the heart rate response to the onset of exercise. In contrast, neither heart rate nor heart rate variability was altered in the sedentary dogs. These data suggest that exercise training enhanced baseline heart rate variability (i.e., all 3 indexes of cardiac vagal activity increased) and attenuated the heart rate response to the onset of exercise. However, the change in the indexes of cardiac vagal activity during exercise onset was similar both before and after the 10-wk exercise training program. As such, reductions in cardiac sympathetic activity most likely also contributed to the attenuated heart rate response to the onset of exercise following the completion of the 10-wk exercise training program.

**Heart rate recovery: training effects.** The heart rate and heart rate variability responses following the termination of
Exercise before and after exercise training are shown in Fig. 3, while the same data before and at the of the 10-wk sedentary period are shown in Fig. 4. These data were obtained during (time = 0 s; with the animals running at 6.4 kph/16% grade) and following the last 30 s of the exercise stress test. Heart rate significantly decreased following the end of exercise (time effect, $F_{3,27} = 248.24$, $P < 0.0001$) with a much more rapid recovery (greater rate of heart rate reduction) noted following training (pretraining-posttraining effect, $F_{1,9} = 8.38$, $P = 0.02$). However, because training provoked reductions in the peak exercise heart rate response, the change in heart rate following the termination of exercise was similar (pretraining-posttraining time interaction, $F_{3,27} = 0.24$, $P = 0.89$, NS) before and after training (heart rate reduction 60 s after the termination of exercise: pretraining $59.8 \pm 2.9$ vs. posttraining $57.8 \pm 5.1$ beats/min) (Fig. 3). The heart rate decrease following exercise was accompanied by corresponding increases in all three indexes of heart rate variability (i.e., increases in indexes of cardiac vagal activity) as displayed in Fig. 3. For example, exercise onset provoked large increases (time effect, $F_{3,27} = 7.4$, $P < 0.001$) in the high-frequency component of the R-R interval variability with larger (pretraining-posttraining effect $F_{1,9} = 8.98$, $P < 0.02$) reductions noted after exercise training. Cardiac vagal activity was maintained to a greater extent (i.e., higher values postexercise training compared with pretraining values) during submaximal exercise following exercise training (Fig. 3). As a consequence, the change in the cardiac vagal activity index following the termination of exercise was similar (pretraining-posttraining $\times$ time interaction, $F_{3,27} = 0.57$, $P = 0.64$, NS) before and after training (cardiac vagal activity index increase 60 s after the termination of exercise: pretraining $2.1 \pm 0.4$ vs. posttraining $1.8 \pm 1.0$ ln ms$^2$) (Fig. 3). Similar results were obtained for R-R interval range and standard deviation of R-R interval (see Fig. 3).

In contrast, although heart rate decreased (time effect, $F_{3,24} = 48.46$, $P < 0.0001$) and heart rate variability increased (e.g., vagal activity index; time effect, $F_{3,24} = 14.95$, $P < 0.0001$) following the termination of exercise, these changes were not altered during the 10-wk sedentary period (pretraining-posttraining effect: heart rate, $F_{1,8} = 0.02$, $P = 0.89$, NS, cardiac vagal activity index, $F_{1,8} = 2.49$, $P = 0.16$, NS) (Fig. 4).

The effects of atropine on the heart rate and heart rate variability responses to the termination of exercise before and after the 10-wk exercise-training program are shown in Fig. 5. The injection of atropine while the dogs were running elicited large increases in heart rate that were accompanied by large decreases in heart rate variability. After the completion of the 10-wk exercise training program, the termination of exercise provoked significantly larger reductions (i.e., a faster recovery) in heart rate that were accompanied by correspondingly larger increases in the various indexes of cardiac vagal regulation. *$P < 0.05$ preexercise training (gray bars) vs. postexercise training (black bars)
reductions in heart rate variability (all 3 indexes of cardiac vagal activity) both before and at the end of the 10-wk exercise training program (e.g., time effect: heart rate, $F_{4,24} = 44.6$, $P < 0.0001$; cardiac vagal activity index, $F_{4,24} = 21.16$, $P < 0.0001$). In addition, exercise training significantly reduced the preatropine heart rate (pre-post effect $F_{1,6} = 8.25$, $P < 0.03$) and all three indexes of heart rate variability (e.g., cardiac vagal activity index, $F_{1,6} = 14.53$, $P < 0.009$). As a consequence of these changes in the preatropine values, the atropine injection elicited larger increases (time × pretraining-posttraining interaction: $F_{4,24} = 4.96$, $P < 0.005$) in heart rate (atropine induced change in heart rate: pretraining $21.4 \pm 6.4$ vs. posttraining $35.4 \pm 3.8$ beats/min) and reductions heart rate variability (e.g., atropine induced change in cardiac vagal activity index: pretraining $-1.2 \pm 0.3$ vs. posttraining $-2.2 \pm 0.2$ ln ms$^2$).

Atropine also provoked large changes in heart rate and heart rate variability in the sedentary animals (e.g., time effect: heart rate $F_{4,20} = 35.81$, $P < 0.0001$; cardiac vagal activity index $F_{4,20} = 17.02$, $P < 0.0001$). However, neither the atropine nor the change in these variables induced by atropine was altered by the 10-wk sedentary period (i.e., the changes in heart rate and heart rate variability were similar before and at the end of the 10-wk sedentary period), and there were no significant pretreatment-posttreatment (for heart rate $F_{1,5} = 0.52$, $P = 0.51$, NS) or pretreatment-posttreatment × time interaction (for heart rate $F_{4,20} = 0.78$, $P = 0.56$, NS) effects.

Finally, the rate at which heart rate returned to baseline (preexercise onset levels) was attenuated by atropine to a similar extent for both the sedentary and exercise-trained animals such that there were no longer differences between the two groups of animals (group × time interaction $F_{4,44} = 1.77$, $P = 0.15$, NS) following the atropine treatment. When considered together, these data suggest that exercise training enhanced cardiac vagal activity and accelerated the heart rate recovery (i.e., the return toward baseline preexercise onset levels) following the termination of exercise. In contrast, these variables were not altered in the sedentary dogs.

Confirmation of exercise training and effects on susceptibility to ventricular fibrillation. Our laboratory has previously reported that the exercise-training program used in the present study provoked significant cardiac and skeletal muscle adaptations (8, 10). For the animals used in the present study, exercise training tended to increase both left ventricular systolic wall thickness [exercise-trained (n = 10), pretraining $9.9 \pm 0.5$ vs. posttraining $10.9 \pm 0.4$ mm; sedentary (n = 9), presedentary $9.9 \pm 0.3$ vs. postsedentary $9.7 \pm 0.4$ mm, $F_{1,20} = 2.58$, $P = 0.12$, NS] and diaphragm citrate synthase activity.
Exercise training (n = 6), 10.9 ± 1.3 vs. sedentary (n = 4), 9.0 ± 2.0 μM·ml⁻¹·min⁻¹, t = 1.58, P < 0.10, NS]. Exercise training (Fig. 6) also provoked significant reductions in heart rate both before and during submaximal exercise that were accompanied by significant increases in heart rate variability (vagal activity index; i.e., 0.24- to 1.04-Hz component of the R-R interval variability), whereas these variables did not change in the sedentary animals (data not shown). When considered together, these data confirm that the exercise training program was effective (i.e., there were significant skeletal muscle and cardiac adaptations induced by the training program).

As previously reported (8, 10), exercise training completely suppressed ventricular fibrillation induced by the exercise plus ischemia test. In contrast, ventricular fibrillation was still induced in the sedentary animals (n = 7); two animals could not be tested due to failure of the hydraulic occluder. It is also important to note that four dogs in the sedentary group (but none in the exercise training group) died during the 10-wk sedentary period.

DISCUSSION

The present study investigated the effects of a 10-wk endurance exercise-training program on the heart rate and the heart rate variability responses to the onset and the termination of exercise in dogs confirmed to be susceptible to ventricular fibrillation. Exercise training attenuated the heart rate response to exercise onset and enhanced (accelerated) the heart rate return toward baseline values (heart rate recovery) following the termination of exercise. Correspondingly, heart rate variability (indexes of cardiac vagal activity) was also enhanced following exercise training. In marked contrast, neither the heart rate nor the heart rate variability responses to exercise onset or following the termination of exercise were altered in sedentary (time control) animals. Atropine pretreatment eliminated the differences in the indexes of cardiac vagal activity and the heart rate response to the termination of exercise noted between the sedentary and exercise-trained dogs. These data suggest that exercise training improved cardiac vagal activity in animals known to be prone to ventricular fibrillation. As far as we have been able to determine, these findings represent the first demonstration that exercise training can both improve heart rate recovery following submaximal exercise and attenuate the exaggerated heart rate responses to exercise onset in subjects prone to malignant arrhythmias.

Abnormal cardiac autonomic regulation and susceptibility to ventricular fibrillation. As was previously noted, both a large heart rate increase at exercise onset and a slow heart rate...
recovery following the termination of exercise have been linked to an increased susceptibility to ventricular fibrillation. For example, Falcone and coworkers (16) examined the heart rate increase elicited by a standard symptom-limited exercise stress test in 458 patients with documented coronary artery disease. They found that the patients with the largest increase in heart rate (≥12 beats/min above the median value of the distribution) also had a greater risk for adverse cardiovascular events (cardiac death and nonfatal myocardial infarction) during a 3.7- to 9-yr follow-up period. In a similar manner, a depressed heart rate recovery was also associated with a greater risk for adverse cardiovascular events (12, 23, 29, 30, 31, 32).

Of particular note, Nissinen et al. (31) found heart rate recovery to be a predictor of all-cause mortality in a group of 229 post-myocardial infarction patients. The abnormal heart rate responses to exercise onset and termination are believed to result from alterations in the cardiac parasympathetic regulation (1, 8, 15, 16, 35, 41) because the initial rapid decrease in heart rate following exercise or the increase with exercise onset was largely eliminated by the prior treatment with the cholinergic antagonist atropine (6–8, 40, 41). Indeed, the injection of atropine a few minutes before termination of exercise completely eliminated the heart rate recovery differences noted between the susceptible and the resistant dogs (42). Thus an abnormal heart rate response to exercise and/or its termination may identify individuals at risk for malignant arrhythmias.

The restoration of a more normal cardiac autonomic activity should also improve heart rate regulation and thereby potentially reduce the risk for lethal cardiac arrhythmias. However, it is important to emphasize that, to be an effective antiarrhythmic therapy, an intervention must maintain cardiac vagal activity when the heart is stressed, as during myocardial ischemia. Indeed, low doses of cholinergic antagonists paradoxically increased the baseline cardiac vagal activity (24) but failed to maintain this increase in heart rate variability when the heart was stressed either by submaximal exercise or by a coronary artery occlusion (18). As a presumed consequence, this intervention proved to be ineffective in the prevention of lethal arrhythmias induced by acute myocardial ischemia (18, 22).

**Effect of exercise training on cardiac autonomic regulation.** Exercise training can alter autonomic neural balance by both increasing cardiac parasympathetic and decreasing sympathetic activity (2, 8, 11, 17, 27, 41, 43, 45). In both humans and animals the heart rate at submaximal workloads is reduced in trained individuals compared with sedentary controls (2, 8, 11, 41). Furthermore, acetylcholine content and choline acetyltransferase activity is increased in the hearts of trained rats (13). In humans, exercise training can increase heart rate variability in patients recovering from myocardial infarction (25, 26, 28, 36).

We recently demonstrated that exercise training induced large increases in heart rate variability in dogs with healed myocardial infarctions that were confirmed to be prone to...
ventricular fibrillation (8). Importantly, this improved cardiac vagal regulation was maintained even when the hearts of these animals were stressed by either acute myocardial ischemia or by submaximal exercise (8). However, the effects of exercise training on the heart rate and heart rate variability response to exercise onset and/or its termination were not investigated in this (or to the best of our knowledge any other) study. The present study extends these previous studies, demonstrating that exercise training can both attenuate the heart rate response to exercise onset and enhance the heart rate recovery following the termination of exercise. This improved heart rate regulation following exercise training was accompanied by corresponding changes in indexes of cardiac vagal activity.

**Limitations of the study.** It must be acknowledged that in the present study, cardiac vagal regulation was only indirectly evaluated using various measures of heart rate variability. This study did not measure the parasympathetic nerve activity directly. However, previous investigations have verified that heart rate variability provides an accurate representation of parasympathetic function (14, 20, 44). Additionally, and in agreement with previous studies (7, 8), the administration of atropine during exercise provoked large heart rate increases and the indexes of cardiac vagal activity fell to very low (zero in most dogs) values in both the sedentary and the exercise trained animals. These data are consistent with an atropine-induced inhibition of cardiac vagal regulation. Therefore, it is reasonable to conclude that the method used in the present study provided reliable indirect measurements of cardiac parasympathetic regulation.

In addition, it is well established that both respiratory rate and tidal volume can alter heart rate variability (19). As such, differences in the respiratory response following exercise training could indirectly contribute to the differences in the cardiac vagal indexes in the susceptible and resistant animals. Respiratory parameters were not measured in this study because of the profound panting response induced by exercise in both the sedentary and the exercise-trained animals (before and after the 10-wk exercise training or sedentary period). It is possible that, despite the panting, respiratory rate or tidal volume was altered in the trained animals. However, our laboratory previously demonstrated that exercise elicited similar respiratory rate changes in resistant and susceptible dogs and that panting did not alter the same indexes of heart rate variability used in the present study (7). It seems unlikely that training-induced changes in respiration can explain heart rate variability noted in the present study.

The mechanisms by which exercise training prevented ventricular fibrillation remain to be determined. The present study suggests that alterations in cardiac autonomic regulation could contribute significantly to this protection. Exercise training enhanced cardiac vagal activation both during the onset and the termination of exercise. However, we previously (8) demonstrated that, although atropine treatment induced large increases in heart rate accompanied by large reductions in heart rate variability, this intervention failed to reintroduce malignant arrhythmias in the majority of the exercise-trained dogs (atropine treatment only resulted in ventricular fibrillation in 1 of 8 animals tested). Clearly, exercise training-induced increases in cardiac vagal activity were not solely responsible for the prevention of ischemia-induced arrhythmias in trained animals. Other factors must play a more central role in the protection that results from training. Our laboratory previously reported that dogs susceptible to ventricular fibrillation, in addition to reduced cardiac vagal control, exhibit an enhanced β₂-adrenergic receptor activation that is reduced by exercise training (10). It is possible that exercise training improves β-adrenergic receptor balance by reducing this enhanced β₂-adrenergic receptor activation and could, thereby, remove the trigger for malignant arrhythmias (due to β₂-adrenergic receptor-mediated increases in myocyte calcium levels) induced by myocardial ischemia. It is also possible that training could alter exercise- and/or ischemia-induced changes in blood potassium (perhaps via changes in skeletal muscle potassium handling) and thereby improve cardiac electrical stability (37). Because blood potassium levels were not measured in the present study, any contribution of altered potassium handling to the exercise training-induced protection from ventricular fibrillation remains to be determined (5, 9, 33, 39, 40).

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**REFERENCES**

EXERCISE TRAINING IMPROVES HEART RATE REGULATION


